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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,460	09/28/2006	Yoko Yamagata	56861	9304

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EXAMINER
BURKHART, MICHAEL D

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/599,460	**Applicant(s)** YAMAGATA ET AL.	
	Examiner Michael Burkhart	**Art Unit** 1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 13 May 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,2,7-9 and 18-23*.
   Claim(s) withdrawn from consideration: *5, 6 and 14-17*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Michael Burkhart/
Primary Examiner, Art Unit 1633

Continuation of 3. NOTE: Claims 24 and 25 are new and thus require new consideration and search for this reason alone. Claims 1 and 9 have been amended such that a specific substitution mutation (K42R) is recited, whereas previously the claims had specified any mutation in the CaMKIIalpha catalytic domain, and dependent claims (e.g. claim 20) had specified K42, but not K42R. This requires new search and consideration of, at the least, the art of record and of the specification for an enabling disclosure of the claimed scope of animals and cells.

Continuation of 11. does NOT place the application in condition for allowance because: Claims 1, 2, 7-9 and 18-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elgersma et al (Neuron, 2002), Wang et al (PNAS, 2003), Hanson et al (Neuron, 1994) and Sutoo et al (Brain Res., 2002). This rejection is maintained for reasons made of record in the Office Actions dated 7/9/2009, 2/18/2010, and for reasons set forth below.

Response to Arguments

Applicant's arguments filed 5/13/2010 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) none of the cited documents teaches an animal expressing the claimed inactive CaMKIIalpha; 2) Elgersma et al do not teach an inactive CaMKII having a modified residue in the catalytic domain; 3) Wang et al teach an F89G, also outside the scope of the instant claims; 4) the K42M/R mutations of Hanson et al are not taught to multimerize with other CaMKIIalpha proteins, and only teach results in cell lines; 5) the prior art does not provide a predictable means for generating the claimed animals, nor healthy knock-in animals; 6) surprising results of CaMKIIalpha expression levels were obtained.

Regarding 1), this is not a 35 USC 102 rejection. The logic of this assertion is thus unclear and unconvincing.

Regarding 2), this was stipulated in the last Office Action. Elgersma et al was not relied upon to teach this claim limitation in this 35 USC 103 rejection.

Regarding 3), this, again, is stipulated. Wang et al was not relied upon to teach this claim limitation in this 35 USC 103 rejection.

Regarding 4), this assertion is false on its face, as it is not accompanied by any facts or scientific reasoning, in contrast to the results of Hanson et al (published in a peer-reviewed journal). Hanson et al teach that no modifications were made in the association domain of CaMKIIalpha (Fig. 1a), thus, it is not clear why any negative effects would be expected on the ability of the mutant to multimerize, as this is the domain responsible. Further, it has been explained that the K42 mutants maintained the ability to multimerize with other CaMKII subunits/isoforms, which may number from 8-10 in the holoenzyme (Hanson et al, page 943, second column). This is all that is required to meet the claim limitation of "a capacity of multimerizing subunits are maintained" , there is no requirement that the claimed CaMKII protein form a "homomultimer" as applicants insist. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., forming "homomultimers") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Regarding 5), again, this assertion is countered by the facts and results in the prior art, not only art cited in this rejection, but supplied by applicants themselves. Applicants appear to want a 35 USC 102 level of disclosure in the prior art whereas this is a 35 USC 103 rejection. There is always some unpredictability about the outcome of complex experiments, particularly those involving in vivo results such as this case. However, there is no technical burden to the creation of the mice (and cells) in the first place, nor in the assessment of the phenotype. Ample motivation to create the mice and cells has been provided and has not been disputed. Given the totality of the prior art teaching that CaMKIIalpha has a prominent role in neuronal activity and learning, it is not surprising that such a complex and broadly worded phenotype as "neuronal activity" is affected in certain areas of the brain but not others. Applicants provide a reference (Kirkwood et al) wherein CaMKIIalpha -/- mice are prepared, and such mice are viable. How then could preparing mice that actually express the CaMKIIalpha protein, albeit harboring a substitution mutation, be unpredictable or difficult when mice that COMPLETELY LACK the protein can be prepared? Applicants are further directed to the results of Elgersma et al wherein mutant CaMKIIalpha knock-in mice are prepared and not associated with any difficulty in breeding. Applicants are inventing problems that do not exist or have been solved by the prior art. That the CaMKIIalpha knock-out mice may be difficult to breed does not mitigate against this rejection as these attempts were obviously successful, and knock-out mice (completely lacking the protein) are difficult to compare to knock-in mutations.

Further regarding 2) - 4), in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding 6), expression levels in knock-in CaMKIIalpha proteins does not appear to be problem, hence, this is not a surprising result. Even if Elgersma et al reduced the levels of CaMKIIalpha by half in their knock-in mice, is this level too low? The CaMKIIalpha mutants of Elgersma et al yielded viable, useful mice. Further, it is not at all clear that using the K42 mutations of Hanson et al to prepare knock-in mice would also yield expression level differences. Finally, it is not a claim limitation, thus, it is unclear how differing CaMKIIalpha expression levels mitigates against rejection of the instant claims that only require CaMKIIalpha expression. The activity of CaMKIIalpha can be partially supplemented by CaMKIIbeta (Giese et al, page 870, middle column). This may explain why differential effects are found in certain areas of the brain when the claimed mutants are used, or it could be that CaMKIIalpha is not required for the measured "neuronal activity" in the cerebral cortex and striatum even though it may be highly expressed in these regions. An example of an unexpected result from using the claimed mice would be that no affects on neuronal activity were found in any part of the CNS, as this would contradict the teachings of the prior art.

Double Patenting

Applicant is advised that should claims 18 or 21 be found allowable, claims 20 and 23 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. This rejection is maintained for reasons made of record in the Office Action dated 2/18/2010, and for reasons set forth below.

Response to Arguments

Applicant's arguments filed 5/13/2010 have been fully considered but they are not persuasive. Applicants essentially assert that the claims have been canceled. This is unconvincing because the claim amendments have not been entered..